

Applicant : Hiroshi Tomiyama et al.

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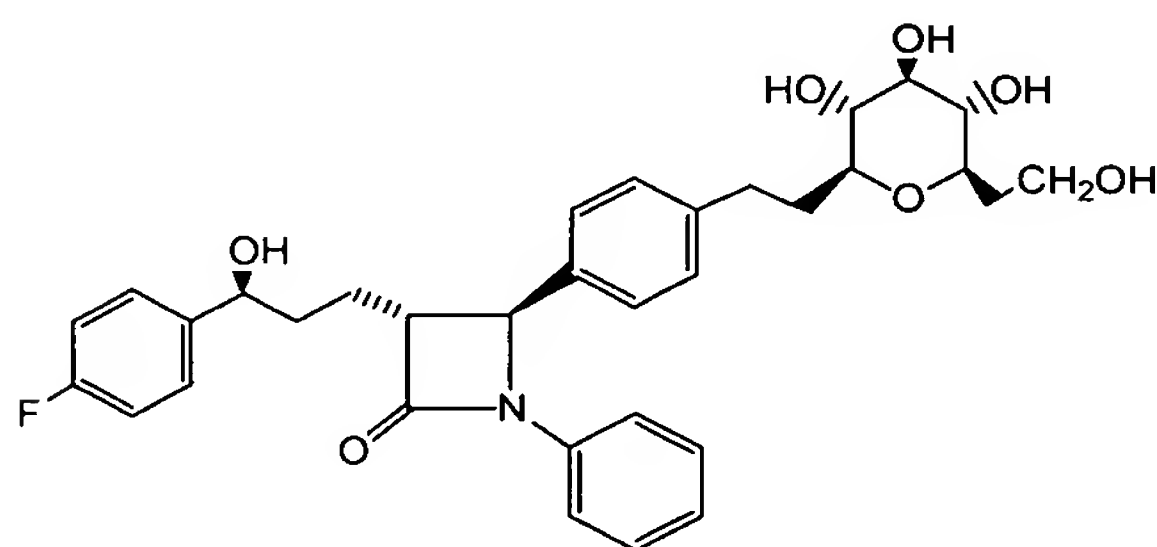
For : SERUM CHOLESTEROL LOWERING AGENT OR PREVENTING OR THERAPEUTIC AGENT  
FOR ATHEROSCLEROSIS



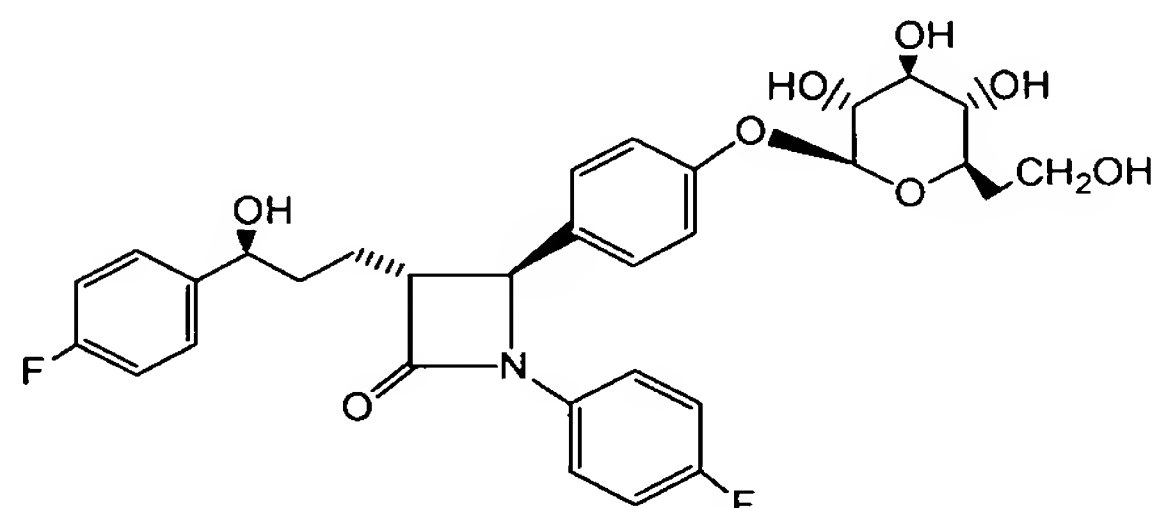
DECLARATION UNDER 37 C.F.R. 1.132

I, Kazuhiro Kosakai, declare as follows :

1. I am named inventor of the above-identified application.
2. The cholesterol lowering effects of C-glycoside compound 56 and O-glycoside compound (synthesized in Kotobuki Pharmaceutical Co., Ltd., Compound A as follows) combined with HMG-CoA reductase inhibitors, were examined using guinea pigs.



Compound 56



Compound A

**【Pharmacological methods】**

Male Hartley guinea pigs were used and fed RC-4 chow (Oriental Yeast Co., Ltd.) ad libitum during the experiment. Compound 56 or compound A with or without HMG-CoA reductase inhibitors dissolved in 0.5 % methylcellulose were administered once a day for 14 days. Twenty hours after the last administration, blood was collected from the vena cava, and serum was separated. The cholesterol value was measured using commercial available kit. The results were shown in Table 1 and 2.

## 【Results】

### ① LDL cholesterol lowering effect

Table 1

Compound	Dose (mg/kg, p.o.)	Lowering rate (%)	Lowering rate versus that of compound 56 or compound A alone (%)
Compound 56	1	-5.2	---
Compound 56 atorvastatin	1 5	14.9	20.1
Compound A	1	1.7	---
Compound A atorvastatin	1 5	11.0	9.3
Compound 56	1	-5.2	---
Compound 56 rosuvastatin	1 5	11.3	16.5
Compound A	1	1.7	---
Compound A rosuvastatin	1 5	10.4	8.7

### ② HDL cholesterol elevating effect

Table 2

Compound	Dose (mg/kg, p.o.)	Elevating rate (%)	Elevating rate versus that of compound 56 or compound A alone (%)
Compound 56	1	-7.6	---
Compound 56 atorvastatin	1 5	7.1	14.7
Compound A	1	-10.4	---
Compound A atorvastatin	1 5	-1.6	8.8
Compound 56	1	-7.6	---
Compound 56 rosuvastatin	1 5	0	7.6
Compound A	1	-10.4	---
Compound A rosuvastatin	1 5	-17.5	-7.1

## 【Discussion】

As shown in the above results, the LDL cholesterol, which is considered as the cause of atherosclerosis formation, lowering effect of compound 56 with HMG-CoA reductase inhibitors is much effective than those of

compound A with HMG-CoA reductase inhibitors (Table 1). Also, the HDL cholesterol, which prevent the atherosclerosis formation, elevating effect of compound 56 with HMG-CoA reductase inhibitors is much effective than those of compound A with HMG-CoA reductase inhibitors (Table 2). Thus, C-glycoside compound is more effective than O-glycoside compound.

I hereby declare that all statements made herein of my own knowledge are true and belief are believed to be true ; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment , or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

October 15, 2009

Date

Kazuhiko Kounhara